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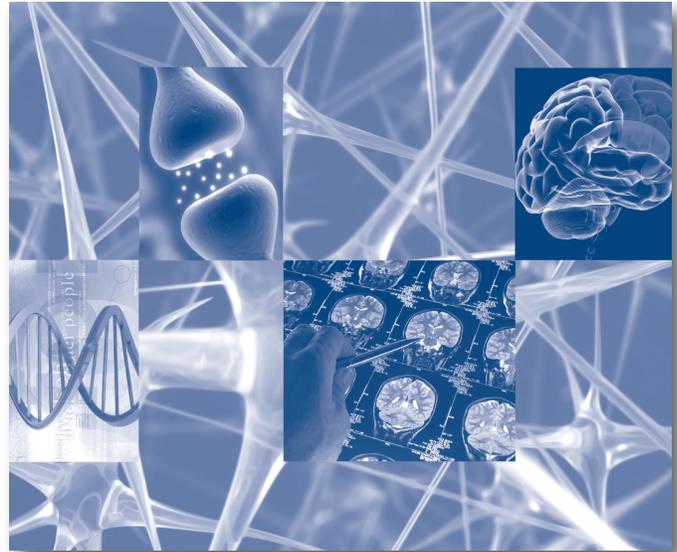
NEUROSCIENCE: PATHWAYS TO ALCOHOL DEPENDENCE

Why does drinking alcohol have such profound effects on thought, mood, and behavior? And why does alcohol dependence develop and persist in some people and not in others? Scientists are addressing these questions and others through neuroscience—the study of the brain, where both alcohol intoxication and dependence begin. Through neuroscience research, scientists are gaining a better understanding of how alcohol changes the brain and how those changes in turn influence certain behaviors.

To function normally, the brain must maintain a careful balance of chemicals called neurotransmitters—small molecules involved in the brain's communication system that ultimately help regulate the body's function and behavior. Just as a heavy weight can tip a scale, alcohol intoxication can alter the delicate balance among different types of neurotransmitter chemicals and can lead to drowsiness, loss of coordination, and euphoria—hallmarks of alcohol intoxication.

Remarkably, with ongoing exposure to alcohol, the brain starts to adapt to these chemical changes. When alcohol is present in the brain for long periods—as with long-term heavy drinking—the brain seeks to compensate for its effects. To restore a balanced state, the function of certain neurotransmitters begins to change so that the brain can perform more normally in the presence of alcohol. These long-term chemical changes are believed to be responsible for the harmful effects of alcohol, such as alcohol dependence.

“When alcohol is present in the brain for long periods—as with long-term heavy drinking—the brain seeks to compensate for its effects.”



Today, thanks to rapidly advancing technology, researchers know more than ever about how alcohol affects the brain and how the brain responds and adapts to these effects. This *Alcohol Alert* summarizes some of what we know about alcohol's short- and long-term effects on the brain and how breakthroughs in neuroscience are leading to better treatments for alcohol-related problems.

HOW ALCOHOL CHANGES THE BRAIN: TOLERANCE AND WITHDRAWAL

As the brain adapts to alcohol's presence over time, a heavy drinker may begin to respond to alcohol differently than someone who drinks only moderately. Some of these changes may be behind alcohol's effects, including alcohol tolerance (i.e., having to drink more in order to become intoxicated) (1) and alcohol withdrawal symptoms. These effects are associated with alcohol dependence.

When the brain is exposed to alcohol, it may become tolerant—or insensitive—to alcohol's effects. Thus, as a person

continues to drink heavily, he or she may need more alcohol than before to become intoxicated. As tolerance increases, drinking may escalate, putting a heavy drinker at risk for a number of health problems—including alcohol dependence.

Even as the brain becomes tolerant to alcohol, other changes in the brain may increase some people's sensitivity to alcohol. Desire for alcohol may transition into a pathological craving for these effects. This craving is strongly associated with alcohol dependence (1).

Other changes in the brain increase a heavy drinker's risk for experiencing alcohol withdrawal—a collection of symptoms that can appear when a person with alcohol dependence suddenly stops drinking. Withdrawal symptoms can be severe, especially during the 48 hours immediately follow-

ing a bout of drinking. Typical symptoms include profuse sweating, racing heart rate, and feelings of restlessness and anxiety (2). Research shows that alcohol-dependent people may continue drinking to avoid experiencing withdrawal. Feelings of anxiety associated with alcohol withdrawal can persist long after the initial withdrawal symptoms have ceased, and some researchers believe that—over the long term—this anxiety is a driving force behind alcohol-use relapse (3).

THE BRAIN'S UNIQUE COMMUNICATION SYSTEM

Tolerance and withdrawal are tangible evidence of alcohol's influence on the brain. Scientists now understand some of the mechanisms that lead to these changes—changes that begin with the brain's unique communication system.

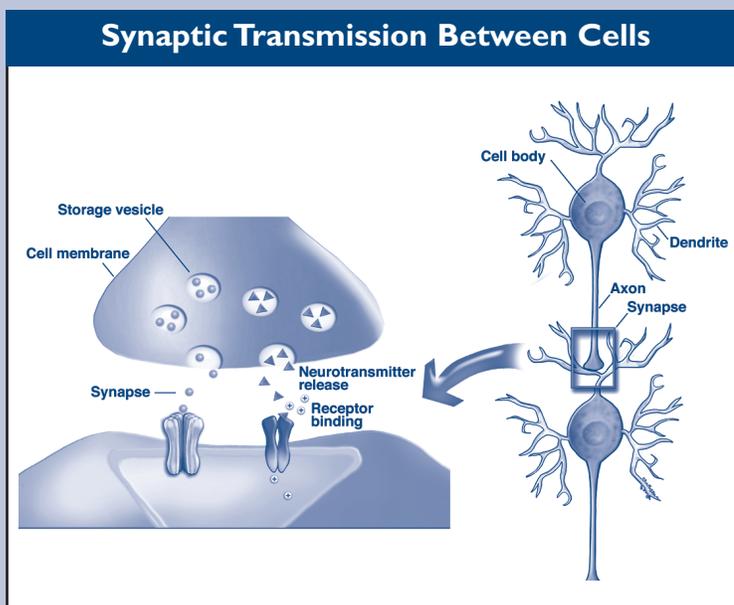
NEURONS AND SYNAPTIC TRANSMISSION

The brain transmits information through a system of interconnected nerve cells known as neurons. Signals travel rapidly along chains of neurons using a combination of electrical and chemical processes. These signals cause many of alcohol's effects on behaviors, such as tolerance, craving, and addiction.

Signals travel from one neuron to the next through a process known as synaptic transmission. Synaptic transmission is made possible by the neuron's unique structure. In addition to a main cell body, neurons have two types of specialized thin branches: axons and dendrites. Axons transmit messages from one neuron to the next, and dendrites receive those messages from nearby neurons. Individual neurons are separated by tiny gaps known as synapses.

Messages travel from one neuron to the next across synaptic gaps and bind to special docking molecules on the receiving neuron's dendrites. These docking molecules are known as neurotransmitter receptors. When a neurotransmitter binds to a receptor, it changes the activity of the receiving neuron.

Depending on the situation, these changes might make the neuron either more likely or less likely to pass on, or "fire," the signal to the next neuron. If the signal is fired, it travels down the axon, sparking the release of more neurotransmitters into the next synapse and passing the signal along to the dendrites of the next neuron. If a signal is not fired, the signal stops.



SOURCE: Lovinger, D.M. Communication networks in the brain: Neurons, receptors, neurotransmitters, and alcohol. *Alcohol Research & Health* 31(3):196–214, 2008.

The brain communicates through a complex system of electrical and chemical signals. These signals are vital to brain function, sending messages throughout the brain, which, in turn, regulate every aspect of the body's function. Neurotransmitter chemicals play a key role in this signal transmission (4).

Under normal circumstances, the brain's balance of neurotransmitters allows the body and brain to function unimpaired. Alcohol can cause changes that upset this balance, impairing brain function. For example, the brain balances the activity of inhibitory neurotransmitters, which work to delay or stop nerve signals, with that of excitatory neurotransmitters, which work to speed up these signals. Alcohol can slow signal transmission in the brain, contributing to some of the effects associated with alcohol intoxication, including sleepiness and sedation.

As the brain grows used to alcohol, it compensates for alcohol's slowing effects by increasing the activity of excitatory neurotransmitters, speeding up signal transmission. In this way, the brain attempts to restore itself to a normal state in the presence of alcohol. If the influence of alcohol is suddenly removed (that is, if a long-term heavy drinker stops drinking suddenly), the brain may have to readjust once again: this may lead to the unpleasant feelings associated with alcohol withdrawal, such as experiencing "the shakes" or increased anxiety.

NEUROTRANSMITTERS: A KEY TO EFFECTIVE MEDICATIONS FOR ALCOHOLISM

As researchers learn more about how neurotransmitters are involved in addiction, they can develop more effective medications that target specific neurotransmitter systems.

Unfortunately, there is no "magic bullet" for treating alcohol-related problems. It is unclear why some people respond well to certain medications, but others do not. However, exciting new research is helping scientists learn more about how alcohol affects different people. A handful of medications are now available to treat alcohol problems, many of which aim to alter

the short- or long-term effects of alcohol by either interfering with or imitating the actions of key neurotransmitters.

The table on page 4 provides information on some of the drugs used to treat alcohol withdrawal and dependence as well as brief descriptions of the neurotransmitter systems the drugs target. Scientists still are seeking to understand the details of how some of these medications work in the brain, but studies suggest that, in some people, they can be helpful in treating alcoholism and its consequences.

NEW STRATEGIES FOR STUDYING ALCOHOL AND THE BRAIN

Powerful imaging methods now allow researchers to study how alcohol affects different brain systems and structures. Some of these methods include positron emission tomography (PET), event-related potentials (ERPs), and magnetic resonance imaging and magnetic resonance spectroscopy (MRI/MRS). These methods are especially useful because they allow researchers to see, in real time, how alcohol changes the human brain. These imaging techniques—when used with alcoholics, nonalcoholics, and children of alcoholics—may help identify genetic risk factors for alcoholism (5).

PET is being used to track the changes that alcohol use causes in specific neurotransmitter systems—changes that may be the cause of alcohol's short-term pleasurable effects (i.e., intoxication) and long-term detrimental effects (i.e., alcohol dependence) (6). PET technology allows researchers to see how these molecules behave. For example, researchers are using PET to track the activity of dopamine, a neurotransmitter believed to contribute to alcoholism. With this information, researchers can identify specific parts of the dopamine system that could be targeted for the development of medications to treat alcoholism (6).

Using ERP, researchers have identified markers that appear in the brains of alcoholics and in children of alcoholics (a population that is at high risk for developing alcoholism) (7; for a review, see 8). A marker is a distinct characteristic that can be associated with a certain group of people. Such markers may be useful for identifying people who are at risk

for alcoholism. For example, scientists have found that certain electrical currents in the brain (as measured by a brainwave called P300) are different in people who are at risk for alcoholism. Research shows that alcoholics have a blunted P300 brainwave; that is, the peak of the brainwave is much lower than in people without an alcohol use disorder. Moreover, this difference in P300 peak is evident in children of alcoholics even before they have taken their first drink. Certain markers linked to alcoholism also are

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MEDICATIONS FOR ALCOHOLISM

Food and Drug Administration Approved Medications	Treatment Use	Target Neurotransmitters	Effect
Benzodiazepines (Valium [®] and Xanax [®])	Treating alcohol withdrawal	GABA (γ -aminobutyric acid)	Increases GABA activity, curbing the brain's "excitability" during its withdrawal from alcohol, allowing the brain to restore its natural balance.
Disulfiram (Antabuse [®])	Preventing alcohol consumption	Main effect on alcohol metabolism rather than in the brain	Increases the concentration of acetaldehyde, a toxic byproduct that occurs when alcohol is broken down (i.e., metabolized) in the body. Excess amounts of this byproduct cause unpleasant symptoms, such as nausea and flushing of the skin.
Naltrexone (ReVia [®] , Vivitrol [®] , Naltrel [®])	Reducing/ stopping drinking	Opioids	Blocks opioid receptors involved in the pleasant sensations associated with drinking.
Acamprosate (Campral [®])	Enhancing abstinence	Glutamate	Thought to dampen glutamate activity and may reduce some of the hyper-excitability associated with alcohol withdrawal.

Promising Medications*	Original Use	Target Neurotransmitters	Potential Use
Topiramate (Topamax [®])	Treating seizures	GABA and glutamate	Appears effective in reducing drinking in alcohol-dependent patients.
Selective serotonin reuptake inhibitors (SSRIs) (fluoxetine [Prozac [®]], sertraline [Zoloft [®]], and others)	Treating depression and anxiety	Serotonin	SSRIs have shown mixed results for treating alcoholics with depression. May reduce drinking in patients who developed alcohol dependence later in life.
Ondansetron (Zofran [®])	Preventing nausea and vomiting	Serotonin	May reduce drinking in patients who developed alcohol dependence early in life.
Baclofen (Kemstro [®] , Lioresal [®])	Treating muscle spasms	GABA	May have beneficial effects in encouraging abstinence, especially in alcoholic patients with liver cirrhosis.
Quetiapine (Seroquel [®])	Sometimes used in treating psychiatric disorders	Dopamine and serotonin	Early-stage trials indicate quetiapine might be effective in increasing rates of abstinence, and to be especially useful in patients with severe alcoholism or in those who developed alcohol dependence early in life.

NOTE: *Not yet approved for use in the treatment of alcohol use disorders.

SOURCES: Lovinger, D.M. Communication networks in the brain: Neurons, receptors, neurotransmitters, and alcohol. *Alcohol Research & Health* 31(3):196–214, 2008.
 Krishnan-Sarin, S.; O'Malley, S.; and Krystal, J.H. Treatment implications: Using neuroscience to guide the development of new pharmacotherapies for alcoholism. *Alcohol Research & Health* 31(4):400–407, 2008.

New Technology to Map Alcohol's Effects

With magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS), researchers use a powerful magnetic field to generate a highly detailed “map” of the brain. For example, one technique, known as functional MRI (fMRI), allows researchers to “see” blood flow to specific regions in the brain and, thus, to identify which regions of the brain currently are active. Using this technique, researchers are exploring how alcohol affects brain function and how brain function changes as alcohol dependence develops over time (9).

found with other mental health disorders, including drug use disorders, antisocial personality disorder, conduct disorder, and attention deficit hyperactivity disorder (for a review, see 8), suggesting that there may be a genetic connection among all of these disorders.

In addition to imaging studies, researchers also are using animals to study alcoholism. The results of these studies can help researchers better understand how to treat alcoholism in humans. In particular, animal models help scientists study the genetic links involved in alcoholism. Researchers can “turn off” genes that may be involved in alcohol addiction in laboratory animals, giving them insight into how these genes affect an animal’s behavior (10). For example, an animal model could show whether an animal will still seek alcohol once a specific gene has been turned off. Researchers also are able to work with small clusters of cells from animal brains and to study alcohol’s effects on a cellular level (11).

Animal studies allow researchers to explore how alcohol damages the brain and how the brain begins to recover from this damage with abstinence from drinking. Studies in rats show that heavy episodic drinking (i.e., “binge drinking”) can injure the brain by causing the death of neurons and other components (12). These brain injuries may cause some of the changes in thought and behavior that are associated with alcohol dependence in humans (13). Animal studies

suggest that the brain can recover at least partially from this damage. One method being investigated is the use of neural stem cells, which, over time, may help to rewire new neurons and repair damage to the brain’s communication system (14).

CONCLUSION

Neuroscience is showing that the pathways of addiction are based in the brain. Using advanced techniques such as imaging methods and studies with animal models, researchers are learning more about how alcohol interacts with the brain’s communication system in different people. Innovative technology also is helping identify the changes that occur in the brain’s structure and function as a result of drinking, and how alcohol disrupts the brain’s delicate chemical balance. This information may help scientists understand why and how alcoholism develops in different populations and ultimately result in more effective and targeted therapies for alcohol abuse and dependence.

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Resources

Source material for this *Alcohol Alert* originally appeared in *Alcohol Research & Health*, Volume 31, Number 3, 2008 and *Alcohol Research & Health*, Volume 31, Number 4, 2008.

- ▶ *Alcohol Research and Health 31(3): Neuroscience: Pathways to Alcohol Dependence Part I—Overview of the Neurobiology of Dependence.* The first issue in this special two-part series introduces what we know about alcohol's effects on the brain, and how these effects might lead to dependence. Articles explore the brain's complex communication systems, and how short- and long-term alcohol use can affect these systems. A special section highlights emerging technologies, such as brain imaging and animal studies, which are helping researchers to understand even more about alcohol's effects on the brain.
- ▶ *Alcohol Research and Health 31(4): Neuroscience: Pathways to Alcohol Dependence Part II—Neuroadaptation, Risk, and Recovery.* The second issue in this series describes how the brain's own adaptations to the presence of alcohol may play a key role in alcohol dependence, and how neuroscience is helping researchers target medications to help people at risk for alcohol use disorders. Other articles show how changes in the brain may lead to tolerance, withdrawal, and relapse to drinking.
- ▶ For these and other resources, visit NIAAA's Web site, www.niaaa.nih.gov



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